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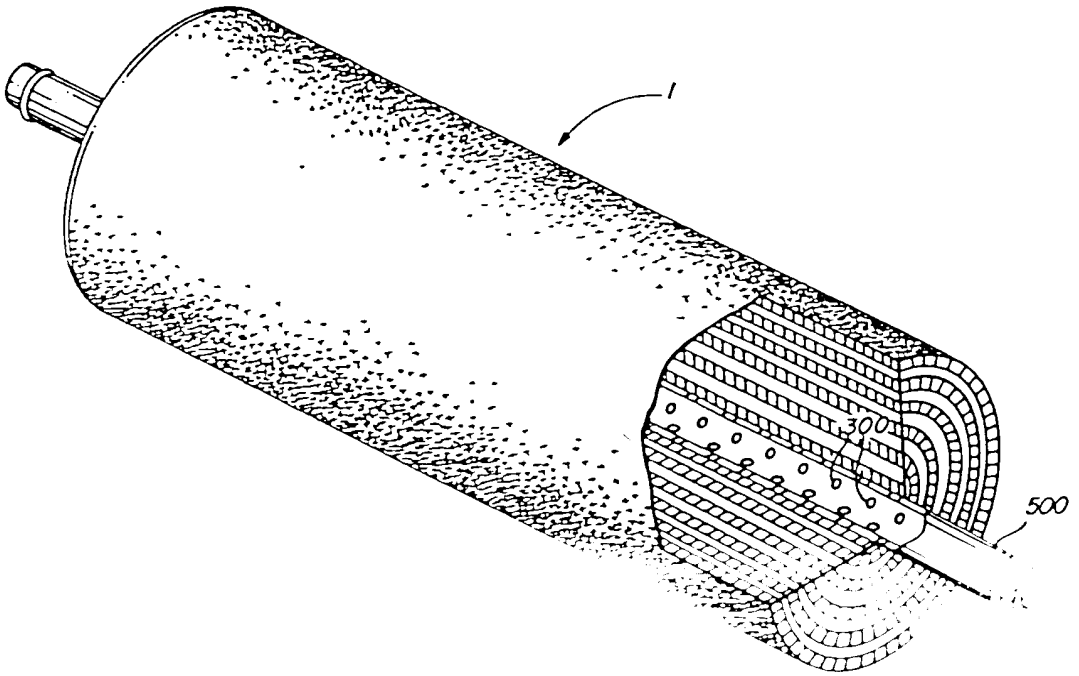

(57) Abstract

Method and apparatus for continuous ultrafiltration of complex fluids having components which degrade the filter characteristics. The improved apparatus and method includes the use of one or more techniques to increase the filtration efficiency. The method and apparatus [illegible] intermediate size or weight components from the complex fluid. By use these improvements, [illegible] complex fluids may be [illegible] diate components is enabled.

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METHOD AND APPARATUS FOR HIGH-EFFICIENCY ULTRAFILTRATION OF COMPLEX FLUIDS

BACKGROUND OF THE INVENTION

1. Field of the Invention

The invention relates generally to improved efficiency ultrafiltration of a fluid having a broad range of component size distribution and, in addition, to removal of an intermediate-size component from a fluid having a complex composition with components which impede filtration.

2. Related Application

This application is in part closely related to the copending application "Method and Apparatus for Treating Blood and the Like", filed on even date herewith, and having a common inventive entity.

3. Description of the Prior Art

Historically, filtration comprehended removal of the larger particles or compounds from a feed fluid by its passage through [illegible] where the feed fluid flow is solely

called batch filtration, and the filter eventually clogs due to accumulation of large particles or compounds in or near the pores. When clogging occurs, the filtration becomes inefficient in the sense that either substantially greater pressure drops are required to maintain a given filtrate rate or the initial filtrate rate cannot be approached. Inefficiency can also result from osmotically-derived back pressures in cases where the feedstock fluid comprises a solution of low to moderate molecular weight compounds, some of which are rejected by the filter membrane (i.e. concentration polarization).

A known alternative to batch filtration is to pass at least a portion of the feed fluid parallel to the local plane of the filter. This technique is useful, for example, where the fluid is a mixture of two substances consisting of molecules of different sizes (size being approximately proportional to the molecular weight, MW) the larger of which is substantially rejected by the filter membrane.

Molecular size is collected through a circulation path parallel to the filter membrane while the filtrate comprising the fluid of smaller molecular size is collected after passage through the membrane under the influence of a transmembrane pressure difference. A second example is a feed fluid containing cells such as bacteria, white blood cells, red blood

the separation of the cells from solution or solvent. Subsequent steps may include the further separation of the compounds in solution as discussed thereinbefore and hereinafter. We use the term convective filtration where there is substantial flow parallel to the filter.

For a complex feed fluid comprising, for example a combination of solutes, suspensions, and perhaps fluids of different molecular sizes, convective and batch filtration both have clogging problems resulting in inefficiency. As will be discussed in more detail hereinafter, a second major problems is that the molecular weight distribution of the filtrate may also change with the inefficiency. Where a filter is required to discriminate at a predetermined molecular or particle size, control over the process is tenuous. Thus, increases in transmembrane pressure to counteract the clogging proclivity and maintain acceptable filtrate rates leads to a modified MW distribution in the filtrate which is not acceptable for many applications.

As a single example of a fluid for which filtration techniques are presently inadequate, consider human (or animal) blood. As shown in Figure 7, blood comprises an extremely broad molecular weight (MW) distribution of components alone with a distribution of cell sizes. As described in the copending application cited hereinbefore, treatment of a kidney patient

requires accurate removal of a minor fraction low and middle molecular weight species at relatively low filtration pressures. Similarly, other common fluids have filtration problems which may be ameliorated by the methods and appraratus described in this application.

SUMMARY OF THE INVENTION

It is an object of the present invention to provide improved apparatus and methods for the efficient ultrafiltration of fluids having a broad range of component sizes whereby reasonable filtrate rates and stable filtration characteristics may be achieved.

It is the further object of this invention to provide improved apparatus and methods for the efficient ultrafiltration of fluids having a broad range of component sizes whereby reasonable filtrate rates and stable filtration characteristics may be achieved in a continuous filtration process.

It is yet another object of this invention to provide an apparatus and a process for the removal of an intermediate fraction from a complex fluid having a broad range of component sizes by a filtration method and apparatus providing for two convective filters of different rejection characteristics.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

through a first convective filter having an intermediate cutoff characteristic and then passing the filtrate from the first convective filter through a second convective filter having a smaller cutoff characteristic, whereby a heavy fraction is obtained from the convective output of the first filter, an intermediate fraction is obtained from the convective output of the second filter, and the light fractin is obtained in the filtrate of the second filter.

In accordance with yet other embodiments of this invention, spectra and pressure-efficient filtration is achieved in convection filters by geometrical and operational augmentation techniques.

In accordance with yet another embodiment of this invention, at least one of the convective filters has a spiral geometry to help prevent clogging of the filter.

In accordance with yet another embodiment of this invention, there is disclosed a method and apparatus for recirculation of any output fraction through the convective filter to improve its efficiency.

The foregoing and other objects, features, and advantages of the invention will be apparent from the following, more particular description of the preferred embodiments of the invention, as illustrated in the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWING

Figure 1 shows the rejection characteristics of exemplary filters for use in this application.

Figure 2 shows schematically a portion of a filter system for removal, as an example, of middle molecular weight material from a feed fluid.

Figure 3 shows the filtrate rate versus pressure characteristics of a filter suitable for removal of low and middle molecular weight materials from a fluid.

Figure 4 shows the clearance or removal rate versus the molecular weight of disolved species as a function of the quantity of rejected materials (e.g. very high molecular weight proteins and/or cells) present on the filter membrane surface.

Figure 5 is a schematic representation of an ultrafiltration system suitable for fluids having a broad range of component distribution.

Figures 6A, 6B and 6C are various views of a filter configuration suitable for use with the present invention.

Figure 7 depicts important components of human blood, including waste materials, as a function of their molecular weight or cell size, as an example of a complex feed fluid.

DETAILED DESCRIPTION

Many biological and industrial fluids consist of a substantial number of components of widely differing sizes or molecular weights (MW). By way of example, the complex spectrum of human blood is shown in Figure 7, where it may be seen that an extremely large number of identifiable components span a molecular size range substantially in excess of five orders of magnitude. In order to filter such a complex fluid to remove a preselected portion of the spectrum, one must pay careful attention to not only both the gross spectral characteristics of the filter(s) but also to the tendency of certain components to clog the filter(s), rendering them pressure inefficient and/or leading to spectral degradation of the filters. Inability to solve these problems for blood has precluded, for example, the practical development of an efficient ultrafiltration system for use as an artifical kidney. Similar problems exist with respect to a great many other complex fluids.

In the so-called batch filtration process, the feed fluid is passed essentially normal to the plane of the filter. For fluid such as water containing suspended sand, batch filtration is feasible as a semi-continuous process because the water can continue to flow through the sand which builds up on the upstream side of the filter and filtration continues with only moderate increases in pressure. Batch filtration is not suitable for

the larger constituents effectively clog the filter and engender large pressure increases for a given filtrate rate. Filtration of such a complex fluid can be made more efficient and continuous by the use of a convective filter where the feed fluid flows approximately parallel to the filter membrane and thus tends to carry off those constituents of the fluid which decrease the filtrate rate. The required flow of filtrate perpendicular to the filter membrane can still cause problems of clogging.

The clogging referred to herein can be two types; surface clogging and membrane pore clogging. Surface clogging is caused by rejected materials which accumulate on the surface (feed fluid side) of the filter membrane. The amount and/or density of this type can be controlled by the methods, devices, and procedures described or referenced in this disclosure. The second type of clogging refers to fluid constituents becoming immeshed within the membrane ultrastructure. This type is, in general, less affected by convective events within the feed channel although there is still possible minor contribution from events within the feed channel. The basic membrane filtration characteristics would be altered in the latter case wherein a different straight line buffered saline limit could be encountered (e.g. the straight line of Figure 3 would be rotated clockwise). The initial technical concepts on membrane pore

during Ultrafiltration" in Transactions of the American Society for Artifical Internal Organs, Vol. 24, Pg. 155, 1978. A more generalized and complete description of multiple limit phenomena supplemental to this disclosure was published in July, 1980 as the chapter entitled, "Ultrafiltration of Plasma and Blood": in the book Advances in Biomedical Enginnering, Part II, entited by D. O. Cooney (Marcel Dekker, Inc., New York and Basel).

Figure 3 shows how surface clogging affects the efficiency of filtration through its influence on the filtrate rate versus transmembrane pressure relationship. In that figure, filtrate rate is linearly proportional to pressure for a "buffered saline" solution. However, when proteins similar to those found in blood are added to the feed fluid, linearity fails and the pressure deviates from the ideal limit very dramatically at and above a certain filtrate rate determined by the nature of the feed fluid, the filter membrane, and the flow conditions (as examples). Figure 3 also shown graphically the definition of efficiency used herein; efficiency is the ratio of the filtrate rate, N_P, on the non-linear curve to the filtrate rate, N_A, on the linear buffered saline curve at the same transmembrane pressure. Note that the efficiency decreases as the pressure is increased. Low efficiency conditions at high pressures can result in gel or precipitate formation on the membrane surface as denoted by the

blood by ultrafiltration have been either unsuccessful or [illegible] major cause of inefficient filters. There are two

major problems. First, while efficiency may be enhanced by moving from say point D to point B in Figure 3 by reducing the pressure and filtrate rate, the rate becomes unacceptably low and may only be increased by making the filter larger. In known configurations of filters for blood applications, area enlargement increases the total amount of protein deposition and in multi-channel designs aggravates the degradation of filtrate rate with time due to concentrating effects. As regions of the filter begin to become ineffective, either the filtrate rate drops or the transmembrane pressure (TMP) increases. The second major problem is that when the filter is operated inefficiently, the composition of the filtrate is modified. This is illustrated by Figure 4 where it may be seen that as the conditions change from points A (no protein) to B, C, and D (increased pressure, protein deposit, and density) in Figure 3 the filtrate includes less and less of the middle molecular weight species. In the case of the kidney application, for example, the clearance rate can drop so low (e.g. curve D) that conventional hemodialysis rates (shown for comparison purposes) are more efficacious than hemofiltration clearances.

Figures 3 and 4 typify the problems of maintaining efficiency and spectral integrity in a convective filter for separation of a fluid into two fractions. It is often the case

characteristics.

It is one of the major features of the present invention to use two or more convective ultrafilters to achieve separation of the intermediate fractions, whereby the intermediate fraction may be removed in a continuous process. Referring now to Figure 1, there is shown the generalized rejection characteristics of two different filter membranes. The type II membrane rejects the heaviest (or largest) particles while passing the intermediate and light fractions, while the type I membrane rejects both the intermediate and largest components and passes the lightest components. Referring now to Figure 2, if two convective filters are interconnected as shown, the light and intermediate fractions are the filtrate of the primary filter (containing the type II membrane); these fractions are then separated in the secondary filter (containing the type I membrane). In the general case shown, all these fractions are available separately as the outputs of a continuous process. Depending on the components present in the filtrate of the primary filter, there can be a filtration efficiency and spectral integrity problem in the operation of the secondary filter as well as in the operation of the primary filter, as hereinbefore described. Various augmentation techniques presented in more detail hereinafter can ameliorate these problems in one or both of these filters.

In order to achieve and maintain efficient ultrafiltration through either or both of the filters in Figure 2, they must be

augmentation herein defined as:

(1) surface perturbations in narrow flow channels

(2) irregular but controlled channel geometries

(3) membrane charge characteristic (repellant)

(4) secondary flow induction by channel inserts (screens, ribbons, etc.)

(5) externally applied forces and/or motions (physical movement, ultrasound, electrical potential, pressure perturbations, pulse flow, etc.)

(6) staging of devices

(7) independent manipulation of flow rates in the device

(8) preferred geometries in combination with augmenting methods

(9) independent control of biochemical and biophysical conditions during filtration.

Referring now to Figure 6, various views of portions of a suitable filter are shown. A complex feed fluid such as blood FF passes through the length L of the filter between the membranes 90. Elements 200 schematically represent a screen which serves to separate the membranes elements 90 by an appropriate distance, to introduce some resistance to flow into the feed fluid path (whereby uniform flow is obtained) and to induce secondary flows which help keep the membrane clean. The model shown contains the membrane cast on a backing [illegible]

(500). For the kidney machine, the total area of the membrane 9 on Figure 5 is desirably on the order of 0.7m2 for average adult intermittent applications. The height H of the feed fluid flow path is desirably in the range 0.25 to 1 mm; too small a value introduces excessive resistance into the feed fluid flow path while too large a value results in inefficient filtration conditions and an impractically large filter.

In order that the convective filters achieve and maintain efficiency, it is imperative that any impediments in the convective path do not appreciably reduce the effective width of the channel (i.e. active membrane) below its nominal value W. For example, if the filter consists of multiple hollow fiber membranes in a parallel arrangement, each with a bore diameter H, rapid plugging of a substantial number of the fibers can occur due to feed fluid concentration and the effective area is unacceptable diminished. Referring to Figure 6A if a local impediment occurs in the channel, the feed fluid must be able to continue to flow both upstream and downstream of the impediment. A rough geometrical criterion for such a condition is that W should be at least as large as L. This requirement is most easily met by spiral filters, which are also compact and relatively easy to fabricate. Referring now to Figures 6B and 6C, there is shown a cross-section of a spiral filter. The [illegible] backing 400

together at the outer edges 66. The envelope and the blood screen 200 are both wound around a central hollow mandrel 500 which serves as a conduit for the filtrate stream. The porous backing 400 from envelope 9 opens only onto holes 300 leading to the hollow portion of the mandrel 500; the filtrate stream passes from the filter unit through the filter perpendicular to the drawing. More details of the construction of a spiral filter may be found in the Westmoreland U.S. Patent 3,367,504, which describes its use for the desalinization of sea water.

Several different combinations of spiral wound construction have resulted in achieving the high efficiency necessary for this application. In looking at the cross section perpendicular to the flow area, prototypes have contained a filtrate mesh spacer. By casting the membrane directly onto a porous, oven, incompressible substrate, the filtrate spacer was eliminated so that existing construction would consist of the feed fluid side spacer and the membrane shown in the drawings herein. The membrane envelope is made by gluing the edges of the porous substrate together with a water-resistant adhesive, such as the urethane glue made by the Uexel Corporation. Other adhesives used in the module construction include medical grade silicone (e.g. Dow Corning Corp.) and possibly polymethylemthacralate or other adhesive strategies common in the field. The substrate materials

also been used with success. Two types of membranes have been developed for this purpose with, apparently, equivalent results. The first type is an asymmetric cellulose acetate somewhat similar to the reverse osmosis membranes developed for desalinization. Unlike the reserve osmosis application, it may be necessary to allow free passage of electrolytes while rejecting the heavy fraction. The membrane may be suitably modified either by formulation and annealing conditions or just by the annealing conditions. Exemplary formulations have been the glycerin perchlorate, cellulose acetate formulation with altered annealing and the cellulose acetate annealed for short periods of time at less than or equal to 80_o Centigrade. The exact annealing conditions will change with different cellulose acetate formulations and still produce an acceptable membrane. The second type of membrane that can be used in hemofiltration is a modification of the newer, thin film composite reverse osmosis technology. The thin film composite reverse osmosis membranes are, typically, a backing similar to the one described above (substate), a polysulfone intermediate membrane, and a thin top film (200-500 Angstroms) on the top of the polysulfone. One top film for reverse osmosis has been a polyamid formulation. The modifications of hemofiltration can be either one of two types. The first is to cast a sufficiently thick polysulfone film with [illegible] characteristics similar to [illegible] given as curve A on figure [illegible] transmission of larger molecules for hemofiltration purposes

molecules normally present in urine. A concomitant membrane criteria would be insignificant passage of molecules at and above 45,000 molecular weight. This is better understood with references to Figure 7, which shows the spectrum of molecules and formed elements in blood. The second modification of the thin film composite reverse osmosis technology would allow a thinner casting of the polysulfone base with an even thinner top film than is used in reverse osmosis. Again, the criteria is easy passage of electrolytes and end products of metabolism with insignificant passage of the larger plasma proteins. All of the modifications outlined above are easily accomplished by technical personnel well versed in membrane technology.

In order to achieve efficient hemofiltration, the feed fluid side spacer 200 must have certain characteristics. Many thick commercial screens will not work due to their ineffectiveness in promoting removal of rejected material away from the membrane surface. Conversely, extremely thin screens can result in too much pressure drop, which detracts from the transmembrane pressure differential. One spacer that has worked is the Vexar, made by DuPont (polyethylene), with 12 strands to the inch and measuring a total thickness of approximately 25 mils. (0.025 inches). The preferred orientation is to have the mesh lines at an approximate angle of 45o to the flow direction as shown in

A preferred casting material to encase the spiral filter and direct the feed fluid and filtrate streams is polycarbonate or an equivalent biocompatible material. The same material has been used for the filtrate collection tube onto which the rolled spiral assembly is wound. The wound assembly is sufficiently smaller than the inside diameter of the polycarbonate housing, to enable potting of the wound assembly into the polycarbonate shell using silicon adhesive.

Filters in accordance with the foregoing description may still not operate efficiently, i.e. without clogging, unless one or more fluid feedback paths are used. For example, if the fluid is blood, it has been found essential for maintenance of efficiency to recirculate a large fraction of the blood exiting the filter at port 5 by reintroducing it at input port 3 at recirculation rate R times the input blood flow rate FF. R must be substantially larger than 2 with a nominal FF of 200 to 250 c/min.; values on the order of 3-8 are required to assure high efficiency with the filter membranes and devices used hitherto and described hereinbefore. While there is at present no comprehensive and exact theoretical basis for the relation of the value of R to the filter parameters and blood composition, most factors are known and at least two factors are believed substantial. First, the use of large amounts of recirculation R

input flow rate range is 200-250 cc/minute with a typical filtrate rate of 80 cc/ minute. Without recirculation, then, the plasma portion of the blood would be depleted of approximately half of its water by the time it reached output port 5. For example, if R = 4, then the filter input flow rate is in the range 1000-1250 cc/minute so that withdrawal of 80-100 cc/minute of water results in a much lower percentage change in blood composition down the length L of the filter. Second, the increased rate of flow through the filter with recirculation apparently results in an increased scrubbing action on the filter membrane whereby its clogging proclivity is reduced. As the blood access limited flow rate is increased, the value of R can be decreased and still achieve high efficiencies.

In a similar manner, either or both the intermediate and light fractions may be recirculated through either or both the convective filters I and II in order to enhance their efficiency. For fluids other than blood which may not contain the heavy (cellular) components which scrub the convective filter to reduce the proclivity to clogging by intermediate components, additive components may be introduced into the feed fluid stream at the input of the convective filter to promote the scrubbing action. Spherical particles will help achieve high efficiency, but may not be as good as non-spherical particles, or particles

In addition to or in lieu of the specific augmentation techniques described above, other efficiency-promoting techniques may be employed. Surface perturbations in narrow flow channels can be achieved in several ways. One is to have the membrane exposed to the feed channel containing surface irregularities which may, as an example, be achieved by casting the membrane over an underlying matrix which would promote the formation of the perturbations in the final membrane product. Another method is to have the membrane supported by an irregular plastic insert with the transmembrane pressure sufficient to deform the membrane over the perturbation which is typically molded into the plastic support. An example of irregular but controlled channel geometries would include tight coiling of the feed channel, periodic or asymmetric surface waviness parallel to the low, or folding of the flow channel, all in a manner to induce flow diversion in the direction of flow. For feed fluids containing charged molecules or particles to be rejected, the membrane can be constructed to contain fixed repellant charges. In addition to the efficiency induction by screens covered in detail, a tubular blood channel can benefit by using a ribbon to produce spiral flow (secondary flows) in addition to axial flow through the tube. Examples of externally applied forces can include, but are not restricted to, the application of surface

membrane or support structure. In this way, a polarization parallel to the filtrate flow aids in repelling the rejected materials away from the membrane surface. Electrodes have been formed by using metallized screens to support the membrane along with a metallized flow channel bounding surface opposite from the surface of the membrane. Another augmentation technique is the use of ultrasound for improving filtration efficiency. In lieu of the metallization, the material must have, as an example, piezoelectric properties. To achieve effective ultrasonic agitation, discrete crystals integral with the filter would be required rather than single continous sound drivers (e.g., reeds or electromagnetically driven diaphragms) which would produce only low frequencies in the feed channel. Ultrasound may be implemented in several ways, including crystals directly exposed to the feed channel. This is the most electrically efficient way of transmitting ultrasound frequency. It is also the least efficient in promoting filtration efficiency while posing the possibility of "heat" damage to the blood. A less electrically efficient way of producing ultrasound is to have the transducer faces placed parallel to the direction of the feed flow, either in or underneath the membrane structure. Although less electrically efficient, the augmentation of filtration by the membrane is most effective with this orientation. Ultrasound

junction. Ultrasound techniques include the use of a single frequency, frequency spectra, and combination of frequencies dependent upon the application. Examples of physical movement include a "washing machine" agitation, continuous rotation with special rotating seals or connectors, or linear vibration, all applied to the entire filtering module. Staging of devices includes the use of more than one device arranged in a parallel and/or sequential manner. This allows direct introduction of cleansed filtrate into the feed flow between each module. This dilutes the feed flow, allowing more efficient filtration in each module, but normally at the price of increased total surface area (more modules) with concomitant improvement in total clearance or effective filtration. These trade-offs are inherent in the implementation of staging and quantative calculations can be made by individuals versed in controlling filtration phenomena. Staging may be of the macrostage variety, in which selected reintroduction of filtrate can be achieved by design along an otherwise continuous flow channel. Staging is also meant to imply any method intermittently "mixing up" the feed stream to eliminate any component polarization within the feed stream. Another variation of staging also found to be effective is the alternating of active and inative filtering areas. This concept somewhat accomplishes the sequential mixing alluded to above. Without any other augmenting method, the remixing would

With the simultaneous use of other augmenting methods, convective modes of transport could assist the diffusion. Independent manipulation of flow rates in the device include, generally, any additional pumping or flow action in addition to the simple throughput required to achieve practical filtration. Details have been given on the use of recirculation in one of the preferred hemofiltration designs, but the invention would also include mechanical oscillatory motions to cause vortex shedding and/or fluid replenishment from grooves perpendicular to the mainstream feed flow, as an example of preferred geometries in combination with other augmentation methods. The more direct example herein is the use of spiral hemofilter modules with screens capable of inducing high efficiency in combination with recirculation of the exiting fluid back to the inlet. Since the hematocrit affects the production of optimum efficiency, variation of the reintroduction of filtrate between the module inlet and exit is also a method of improving the filtering efficiency, considered to be one of the biophysical condition embodiments. In addition to the methods already covered, independent control of biochemical and biophysical conditions includes the pH in the feed channel (more importantly at the membrane surface), control over the charge at the membrane surface, and the fractional filtrate to feed fluid return ratio.

1 micron), auxiliary particles are unnecessary. That is, there is a category of complex fluids containing natural particles, huge macromolecules, or active or inactive cellular material with which efficient filtration may be achieved by the apparatus and methods described with respect to the blood example hereinbefore without the addition of auxiliary particles. Complex fluids in this category comprise human and animal blood or lymph fluids, microbial or cellular suspensions (e.g. bacterial, plant cells, animal blood or lymph fluids, microbial or cellular suspensions (e.g. bacterial, plant cells, animal cells, etc.) meat products and by-products, plant extracts, suspensions of algae or fungi, vegetable food and beverages containing particles such as pulp (e.g. orange juice), pulp products, activated charcoal suspensions, paints, latex suspensions, starch, photographic emulsions, printer's ink, waste streams such as machine oil, automotive oil and other oily suspensions or emulsions which it is desirable to process or reprocess (e.g. reclaim).

Ideal candidates for the apparatus and techniques described in this application include bacterial or other culture media (for the harvesting of the grown components, including proteins) and the removal of antigens, viruses or bacteria from fluid streams.

By way of more specific example, anti-cancer-like substances (e.g. interferon) may be produced by stimulating [illegible] interferon molecule is sufficiently

in Figure 2, where the feed fluid may comprise cell cultures in a broth medium. Interferon is a large, fragile molecule sufficiently bigger in size than the normal nutrients and much smaller than the cells that produce it that it may fit into the strategy of Figure 2 and be removed as an intermediate fraction. The feed fluid in Figure 2 would comprise the live cells or dead cell fragments, the interferon and the nutrient of broth materials. The first filter module in Figure 2 (containing the Type II membrane) would contain, for example, a Nuclepore membrane with a pore size preferably between 0.1 and 0.9 microns. Using recirculation in the spiral wound module cell, as shown in Figure 5, debris accumulation on or near the membrane surface could be reduced and high efficiency filtration conditions established. For this application pulsating flow or pressures may be slightly better than constant flow recirculation. Pores of approximately 0.4 microns and above provide for easy transmission of the interferon and nutrient fluid (broth) while the cellular material is rejected. An advantage to this process is the gentle treatment of the interferon molecule. This is a distinct advantage over present methods of concentrating this valuable substance. The filtrate stream from the type II membrane would then be processed by a second filtrate module where the type I membrane could be

contain only the nutrient materials (the broth in a water solution) and could be returned to the cell growth or interferon producing process as part of the overall process (not shown). The intermediate fraction removal stream from the module with the type I membrane would contain interferon in a more concentrated state than in any other portion of the process shown. This stream might be subject to multi-stage processing with type I modules to gently accomplish further concentrating of the interferon. A unique advantage of this schema is that the filtrate process is gentle, an absolute requirement in interferon production. Interferon production is presently done in batch systems, whereas the filtration, separation, and concentrating of interferon could be made continuous. This is another distinct advantage. The type I filter membrane module for this application would not be particularly susceptible to the efficiency augmentation methods since neither the interferon nor the nutrient broth would contain macromolecules or particles of sufficient size and concentration to engender the high efficiency potential of the augmentation methods.

In a similar fashion, animals may be harvested for antibody production. An antigen would be introduced into the animal (e.g., cow) and the immune system would produce antibodies to the antigen. Antibodies would be either cell mediated or in the [illegible] protein spectra. Following the

producing substantial antibodies. The type II membrane would again be a microporous type for plasmapheresis purposes. There are commercial cellulosic and polysulfone membranes (made by Millipore, Enka, Gelman Corporations and others) with tortuous path structure that can be used in place of the Nuclepore membrane given as an example in the interferon process. Plasma as defined in Figures 7 would pass through the pores while all blood cells would be rejected. The type I membrane is a specially designed ultrafiltration type with transmission of molecules up to approximately 100,000 molecular weight. A charged membrane would augment the separation of the albumin molecules from the globulin molecules while a pH change could also shift the isoelectric points of the proteins to enhance selective separation. Another possible co-process would be gelation of the proteins or cryoprecipitation. A perfect membrane or one employing either an electric field or cross-flow fractionation could accomplish the selective separation of the immunglobulins from the remaining plasma proteins. The unwanted plasma proteins and all lower molecular weight material would be contained in the filtrate stream from the type I membrane and could be returned to the animal. The removal stream would contain concentrated immunoglobulins and could be subject to further processing or concentrating.

of a large molecular weight protein from huge cells which must be kept in a controlled environment. The inherent advantage is that the intermediate fraction removal stream is already encentrated in the protein (refer again to Figure 2) and the culture media and cells can be remixed by combining the heavy and light fraction removal streams. The first separation step in the type II module would be subjected to the high efficiency techniques described hereinbefore and hereinafter, while the second filtrate module containing the type I membrane would not inherently be subject to efficiency augmentation, but could have particles added to it. The same cell separation requirement is inherent in the overall process of using solar energy with photosynthesis to produce high energy molecules which are then useful for food purposes or synfuel (biomass) energy production purposes. Other medical applications include the separation of cerebrospinal fluid and the on-line production of cardioplegia solution.

The foregoing material has described complex fluids having sufficiently large particles or cells so that all the augmentation methods are potentially applicable. Where these large particles or cells are not present, certain of the efficiency inducing techniques relating to the dynamics of the feed fluid channel flow are not very helpful. For such complex fluids, other of the augmentation techniques described are still

to enable the full range of efficiency augmentation techniques described hereinbefore. After the filtration, the auxiliary particles or cells could be removed if desired by additional filtration, centrifugation or other appropriate conventional techniques. Another class of complex feed fluids may have molecules sufficiently small or of such a geometrical configuration that even particle addition could be efficiency inefficacious. Even for this latter class, the double convective filter method and apparatus (possibly in combination with feedback or recirculation techniques, charged membranes, etc.) will provide results superior to existing membrane separation technology. The following is a list of applications or complex fluids containing insufficient cells or particles for the self-induction of all augmentation methods: recombinant genetic engineering products, part of chemical or clinical analysis systems, waste water treatment, cleaning incoming water streams paints, RNA/DNA processing, enzyme engineering, dairy product processing including whey, food processing such as tomato juice, laundry waste or incoming fluid processing, part of the recycling of dry cleaning fluids, gelatin production, wax and wax product processing, production of liquid foods, reprocessing of steel pickle liquor, polymer processing, de-watering of metallic colloids, processing of oily emulsions, and production

parameters are preferred. While homogeneous hard spherical particles will help achieve high efficiency, flexible spherical particles or flexible particles of non-uniform density or shape are more efficacious.

While the invention has been particularly described and shown in reference to the preferred embodiments thereof, it will be understood by those skilled in the art that various changes in form and detail and omissions may be made therein without departing from the spirit and scope of the invention.

We Claim:

1. An apparatus for the filtration of predetermined molecular weight components from a complex fluid, comprising convective filtration means for separation of said fluid into a heavyfraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filtration means including at least one augmentation means for maintaining efficiency during said filtration.

2. An apparatus for the filtration of predetermined molecular weight components from a complex fluid, comprising convective filtration means for separation of said fluid into a first fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said first fraction, said means comprising spiral geometry augmentation means for maintaining efficiency during the period of said filtration.

3. The apparatus of Claim 1 or Claim 2, wherein said filtration means includes at least two augmentation means for maintaining the efficiency of said filtration during the period thereof.

4. The apparatus of any of Claims 1-3, further comprising means for recirculating a portion of said heavy fraction through

5. The apparatus of any of Claims 1-3, further comprising means for recirculating a portion of said filtrate fraction through said convective filtration means to improve filtration efficiency.

6. The apparatus of any of Claims 1-3, wherein said convective filtration means comprises charged membrane means for repelling selected constituents in said blood.

7. The apparatus of any of Claims 1-3, further comprising first recirculation means for recirculating a portion of said heavy fraction through said convective filtration means and second recirculation means for recirculating a portion of said filtrate fraction through said convective filtration means to improve filtration efficiency.

8. An apparatus for the filtration of predetermined molecular weight components from a complex fluid comprising, in combination:

first convective filtration means for separation of said fluid into a heavy fraction having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction; and

second convective filtration means for reception of said filtrate fraction and separation of said filtrate fraction into an intermediate fraction having intermediate molecular weight components and a light fraction having lower molecular weight components than said intermediate fraction.

9. The apparatus of Claim 8, where at least one of said first and second convective filtration means has spiral geometry augmentation means for maintaining efficiency during the period of filtration.

10. The apparatus for Claim 8 or 9, where said first convective filtration means comprises charged membrane means for repelling selected constituents in said blood.

11. The apparatus of any of Claims 8-10, further including recirculation means for recirculating a portion of said heavy fraction through said first filtration means for enhancing efficiency during said separation.

12. The apparatus of any of Claims 8-10, further comprising first recirculation means for recirculation means for recirculating a portion of said heavy fraction through said

convective filtration means, both of said recirculated portions improving filtration efficiency.

13. The apparatus of any of Claims 8-12, further including means for recombining said heavy and said light fractions.

14. A method for separating predetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through a convenctive filter for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight componentsthan said heavy fraction, said filter having at least one augmentation means for maintaining the efficiency of said filtering during the period thereof.

15. A method for separating perdetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through spiral convective filter means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtration fraction having lower molecular weight components than said heavy fraction.

16. The method of any of Claims 17-20, further including recirculating a portion of said heavy fraction through said filtration means to improve filtration efficiency.

17. The method of any of Claims 14-16, further including recirculating a portion of said filtrate fraction through said

18. The method of any of Claims 14-17, said method further comprising the step of exposing said complex fluid in said convective filter means to charged membrane means for repelling selected constituents in said blood.

19. A method for separating predetermined molecular weight components from a complex fluid comprising the steps of:

passing said fluid through first convective filtration means for separating said fluid into a heavy fraction having high molecular weight components and a filtrate fraction having lower molecular weight components than said heavy fraction;

passing at least a portion of said filtrate fraction through second convective filtration means for separating said filtrate portion into an intermediate fraction having intermediate molecular weight components and a light fraction having lower molecular weight components than said intermediate fraction.

20. The method of Claim 19, wherein said fluid is passed through first convective filtration means having a spiral geometry.

21. The method of Claim 19 or Claim 20, further including the step of recirculating a portion of said heavy fraction through said first convective filtration means to enhance the separation efficiency.

22. The step of recirculating a portion of said filtrate fraction

through said first convective filtration means to enhance the separation efficiency.

23. The method of any of Claims 19-22, further including the step of recombining said heavy fraction and said light fraction.

24. The method of any of Claims 19-23, further including the step of removing at least a portion of said intermediate fraction in a continuous process wherein at least portions of said heavy and said light fractions are returned to a generation situs for said complex fluid.

25. An apparatus for the filtration of a complex fluid comprising cellular material, comprising convection filtration means for separation of said fluid into a heavy fraction including said cellular material and a complex filtrate fraction, said filtration means including at least one augmentation means for maintaining efficiency during said filtration.

26. An apparatus for the filtration of a complex fluid comprising cellular material, comprising convection filtration means for separation of said fluid into a heavy fraction including said cellular material and a complex filtrate fraction, said means comprising spiral geometry augmentation means for maintaining efficiency during the period of said

complex fluid, comprising the step of filtering said fluid through a convective filter for separating said fluid into a heavy fraction comprising said cellular components and a complex filtrate fraction, said filter having at least one augmentation means for maintaining efficiency of said filtering during the period therefor.

AMENDED CLAIMS
(received by the International Bureau on 14 September 1982 (14.09.82))

Claim 1. An apparatus for the filtration of predetermined molecular weight components from a complex fluid comprising, in combination:

first convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separation of said fluid into a heavy fraction having high molecular weight components and filtrate fraction having lower molecular weight components than said heavy fraction said first convective filtration means including at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate; and

second convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for reception of said filtrate fraction and separation of said filtrate fraction into an intermediate fraction having intermediate molecular weight components and a light reaction having lower molecular weight components than said intermediate fraction.

2. The apparatus of Claim 1, wherein at least one of said first and second convective filtration means comprises filtrate collection portion means for maintaining efficiency during the period of filtration.

3. The apparatus for Claim 1 or 2, wherein said first filtration means comprises charge membrane means for

4. The apparatus for any one of Claims 1-3, further including recirculation means for recirculating a portion of said heavy fraction through said first filtration means for enhancing efficiency during said separation.

5. The apparatus of any one of Claims 1-3, further comprising first recirculation means for recirculation means for recirculating a portion of said heavy fraction through said first convective filtration means, and second recirculation means for recirculating a portion of said filtate fraction through said first convective filtration means, both of said recirculated portions improving filtration efficiency.

6. The apparatus of any one of Claims 1-5, further including means for recombining said heavy and said light fractions.

7. A method for separating perdetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through spiral convective filter means forhaving a spiral filtrate collelction channel separating said fluid into a heavy fraction having high molecularweight components and complex filtrate fraction having lower molecular weight weight components than said heavy fraction.

8. A method for separating predetermined molecular weight components from a complex fluid comprising the steps of:

passing said fluid through first convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said fluid into a heavy fractaion having high molecular weight components and a filtrate fraction having lower molecular weight weight components than said heavy fraction,said first filtration means including at least one augmentation means for maintaining said filtrate fractiton at a substantially constant rate;

passing at least a portion of said filtrate fraction through second convective fitration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said filtrate portion into an [illegible] having intermediate molecular weight components than said intermediate fraction.

9. The method of Claim 8, wherein said fluid is passed

10. The method of Claim 8 or Claim 9, further including the step of recirculating a portion of said heavy fraction directly to and through said first convective filtration means to enhance said first convective filtration means to enhance the separation efficiency.

11. The method of any one of Claims 8-10, further including the step of recirculating a portion of said filtrate fraction through said first convective filtration means to enhance the separation efficiency.

12. The method of any one of Claims 8-11, further including the step of recombining said heavy fraction and said light fraction.

13. The method of any one of Claims 8-12, further including the step of removing at least a portion of said intermediate fraction in a continuous process wherein at least portions of said heavy and said light fractions are returned to a generation situs for said complex fluid.

14. An apparatus for the filtration of predetermined molecular weight components from a complex fluid, comprising convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separation of said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said convective filtration means including at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate, and means for recirculating a portion of said heavy fraction directly to and through said convective filtration means to improve filtration efficiency.

15. An apparatus for the filtration of predetermine molecular weight components from a complex fluid, comprising convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separation of said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said convective filtration means including at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate, and means for recirculation a portion of said filtrate fraction through said convective

16. An apparatus for the filtration of predetermined molecular weight components from a complex fluid, comprising convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separation of said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said convective filtration means including at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate, said convective filtration means comprises charged membrane means for repeling selected constituents in said complex fluid.

17. The apparatus of Claim 14 further including means for recirculating a portion of said filtrate fraction through said convective filtration means to improve filtration efficiency.

18. The apparatus of any one of Claims 14-17, further including means for recombining said heavy and said light fractions.

19. An apparatus for the filtration of predetermined molecular weight components from a complex fluid, comprising convective filtration means including membrane means and means to direct feed flow substantially parallel to said membrane means for separation of said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said convective filtration means including at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate, and charging means for screening selected constituents in said complex fluid.

20. A method for separating predetermined molecular weight components from a complex fluid, comprising the steps of filtering said fluid through a convective filter including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filter having at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate and recirculating a portion of said heavy fraction directly to and through said filtration means to improve filtration efficiency.

21. A method for separating predetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through a convective filter including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filter having at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate and recirculating a portion of said filtrate fraction through said filtration means to improve filtration efficiency.

22. The method of Claim 21 further including recirculating a portion of said heavy fraction through said filtration means to improve filtration efficiency.

23. A method for separating predetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through a convective filter including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filter having at least one augmentation means for maintaining said filtrate fraction at a substantially [illegible] constituents in said complex fluid.

24. The method of Claim 23 wherein said charged means being charged membrane means for repelling selected constituents in said complex fluid.

25. A method for separating predetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through convective filter including membrane means and means to direct feed flow substantially parallel to said membrane means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filter having at least one augmentation means for maintaining said filtrate fraction at a substantially constant rate, said augmentation means being the application of ultrasonic energy means for avoiding clogging of said convective filter and for maintaining said filtrate fraction at a substantially constant rate.

26. The method of Claims 20 and 21, further including the step of recombining said heavy fraction and said complex filtrate fraction.

27. The method of Claims 20 and 21, further including the step of removing at least a portion of an intermediate fraction [illegible] process wherein at least portions of said heavy

[illegible] generation situs [illegible]

28. A method for separating predetermined molecular weight components from a complex fluid, comprising the step of filtering said fluid through a filter means for separating said fluid into a heavy fraction having high molecular weight components and a complex filtrate fraction having lower molecular weight components than said heavy fraction, said filter means having ultrasonic means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said fluid into said heavy fraction having high molecular weight components and said complex filtrate fraction having lower molecular weight components than said heavy fraction and for maintaining said filtrate fraction at a substantially constant rate.

29. A method for separating a complex fluid having cellular material comprising the step of filtering said fluid through a filter means for separating said fluid into a heavy fraction including said cellular material and a filtrate fraction, said filter means having ultrasonic means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said fluid into said heavy fraction including said cellular material and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate.

30. A method for separating a complex fluid having cellular material comprising the step of filtering said fluid through a filter means for separating said fluid into a heavy fraction including said cellular material and a filtrate fraction, said filter means having charged means for avoiding clogging of said filter means in order to allow said filter means to continue to separate said fluid into said heavy fraction including said cellular material and said filtrate fraction and for maintaining said filtrate fraction at a substantially constant rate.

31. A method for separating a complex fluid having cellular material comprising the step of filtering said fluid through a filter means for separating said fluid into a heavy fraction including said cellular material and a filtrate fraction, and means for recirculating a portion of said heavy fraction including said cellular material directly to and through said filter means.

32. A method for separating a complex fluid having cellular material comprising the step of filtering said fluid through a filter means for separating said fluid into a heavy fraction including said cellular material and a filtrate fraction, and means for recirculating a portion of said filtrate fraction through said filter means.

[illegible]

filter means.

34. A method in accordance with Claim 33 including recombining said heavy fraction including said cellular material and said filtrate fraction.

EDITORIAL NOTE

The applicant failed to renumber the amended claims in accordance with Section 205 of the Administrative Instructions.

In the absence of any specific indication from the applicant as to the correspondence between original and amended claims, these claims are published as filed and as amended.

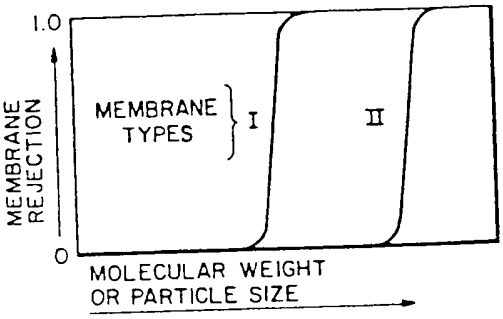


Fig-1

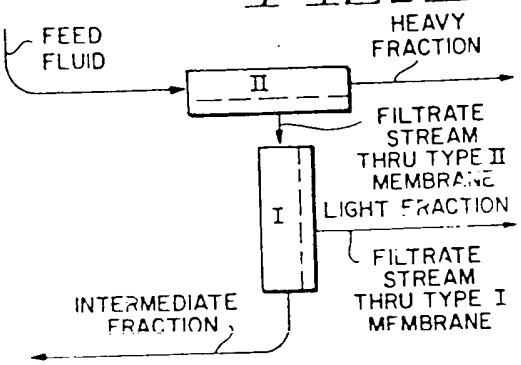


Fig-2

Fig-6C

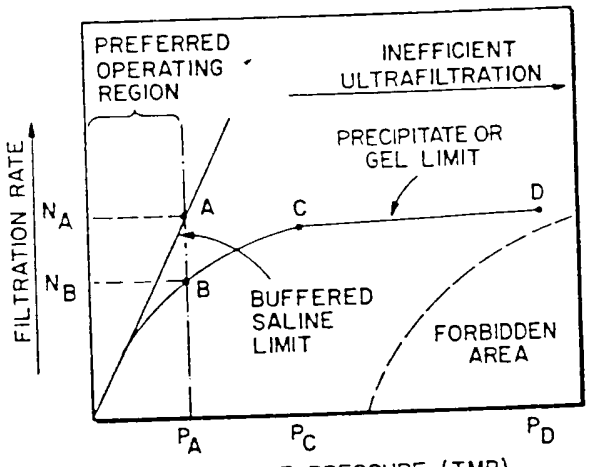
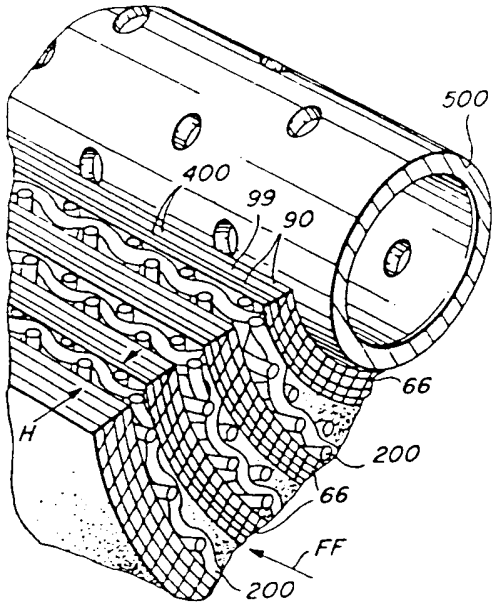


Fig-3



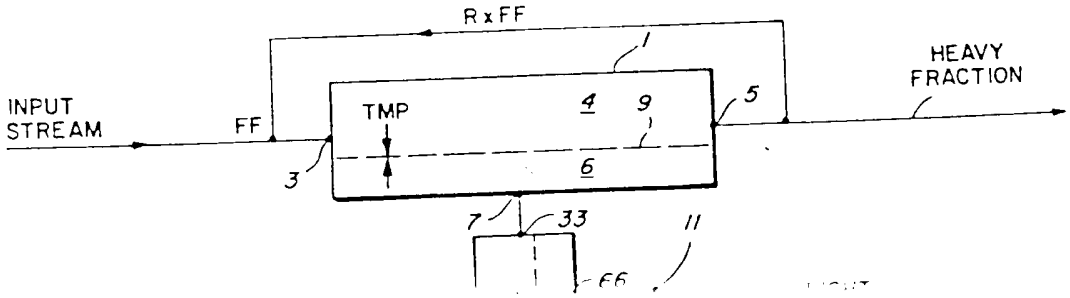


Fig-5

INTERMEDIATE FRACTION

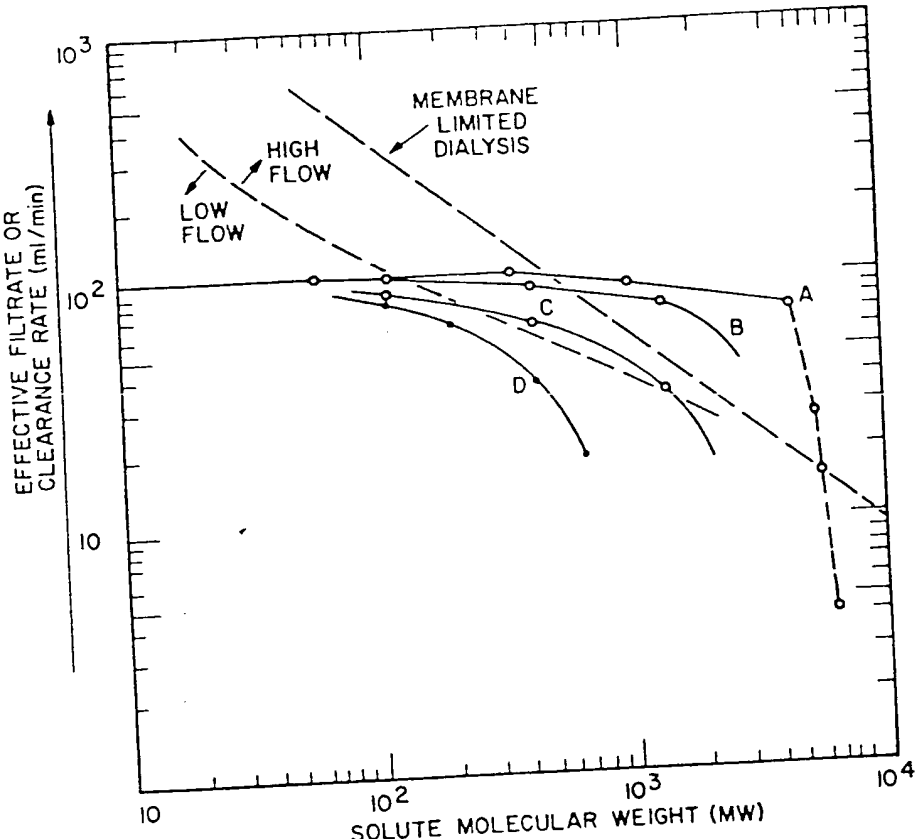
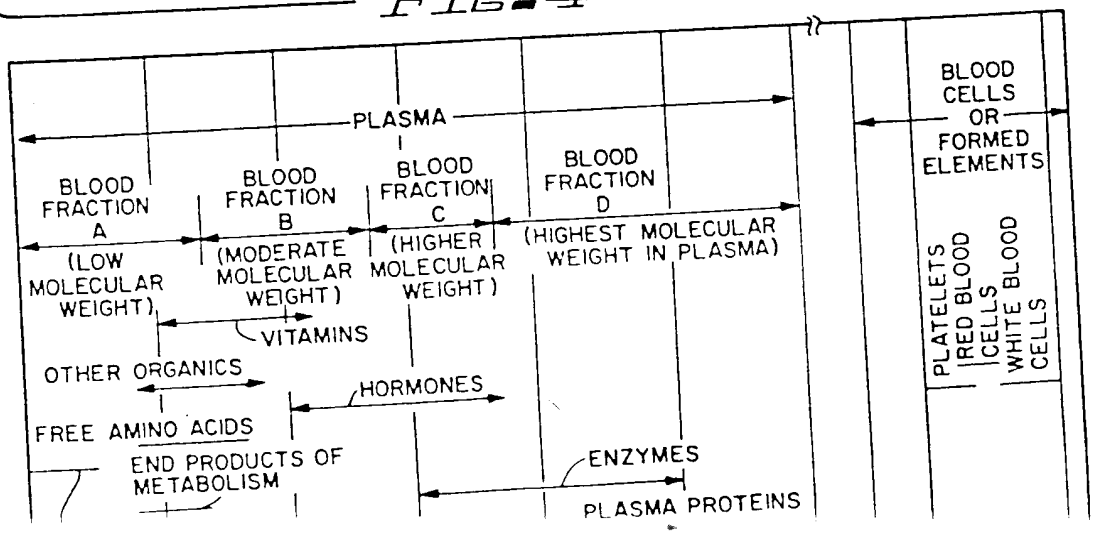


FIG-4



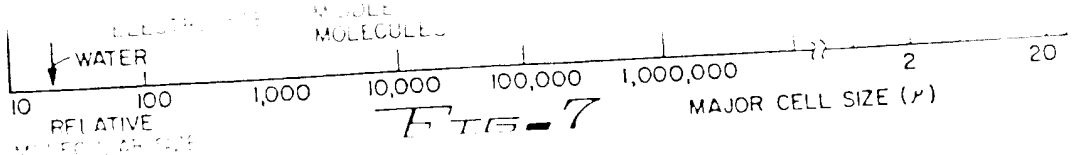


FIG-7

SUBSTITUTE SHEET

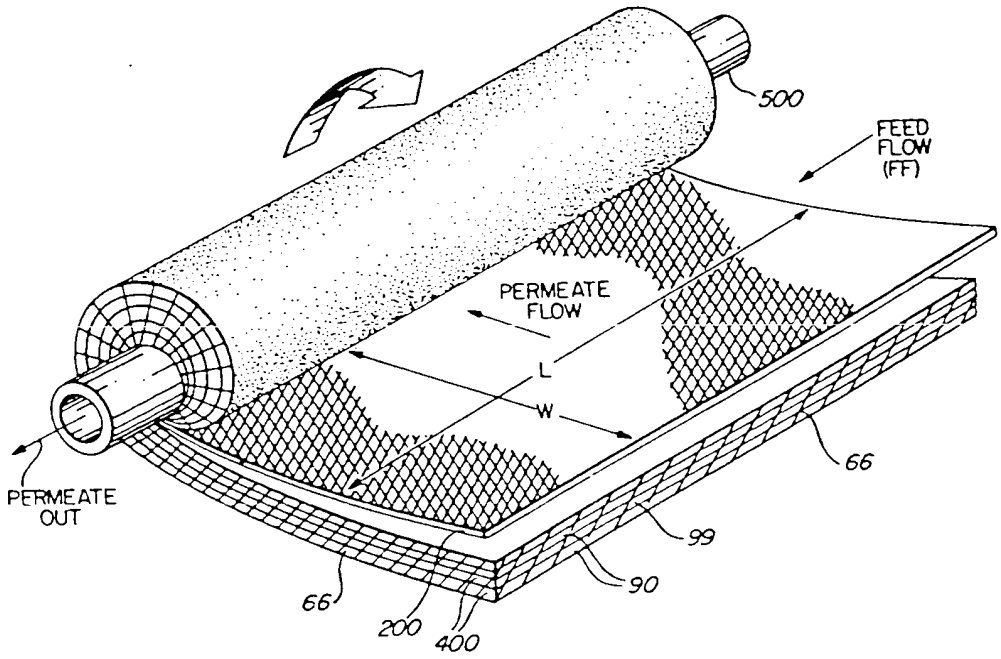


FIG-6A

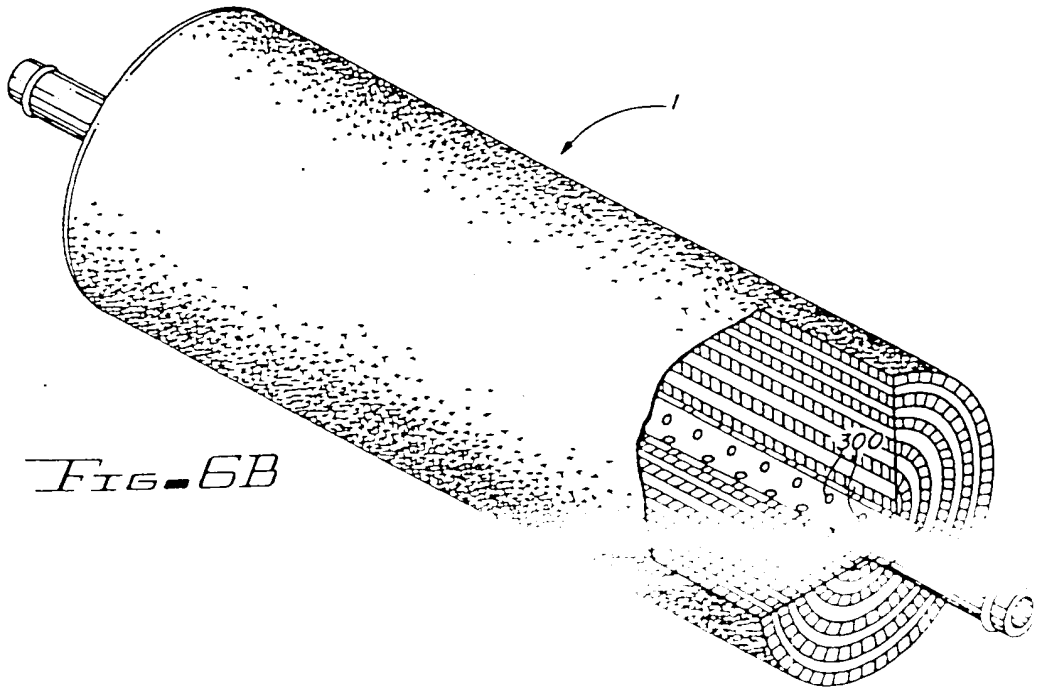


FIG-6B

INTERNATIONAL SEARCH REPORT

International Application No PCT/US82/00450

I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

INT.CL.[3] B01D 13/00, B01D 31/00

U.S. CL. 210/637,641,651,195.2,259,295,335,388,433.2

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
U.S.	210/636,637,641,644-651,767,790,805,806,195.2,257.2,779 210/259,295,321all,335,388,433all,455,456,927

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
X	US, A 3,579,441 PUBLISHED 18 MAY 1971, BROWN.	1-3,8-10,14,15 19-21,25-27
X	US, A 3,705,100 PUBLISHED 5 DECEMBER 1972, BLATT ET AL.	1-3,8-10,14,15, 19-21,25-27
X	N, CHEMICAL TECHNOLOGY, ISSUED JANUARY 1971, M.C. PORTER ET AL, MEMBRANE ULTRAFILTRATION, PAGES 56-63.	8-10,19-21
X	US, A 4,125,462 PUBLISHED 14 NOVEMBER 1978, LATTY.	10
X	N, JOURNAL OF AGRICULTURE AND FOOD CHEMISTRY, ISSUED 1971, W.F. BLATT, MEMBRANE PARTITION CHROMATOGRAPHY: A TOOL FOR FRACTIONATION OF PROTEIN MIXTURES, PAGES 589-594.	8-10,19-21
A	US, A 3,367,504 PUBLISHED 6 FEBRUARY 1968, WESTMORELAND.	
A	US, A 3,483,867 PUBLISHED 16 DECEMBER 1969 MARKOVITZ.	
A	N, TRANSACTIONS OF THE AMERICAN SOCIETY OF ARTIFICIAL INTERNAL ORGANS, VOLUME 14, ISSUED 27 APRIL 1978, W.J. DORSON ET AL, QUANTITATION OF MEMBRANE-PROTEIN SOLUTE INTERACTIONS DURING ULTRAFILTRATIONS, PAGES 155-161.	

* Special categories of cited documents: [15]

"A" document defining the general state of the art

"E" earlier document but published on or after the international filing date

"L" document cited for special reason other than those referred to in the other categories

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but on or after the priority date claimed

"T" later document published on or after the international filing date or priority date and not in conflict with the application, but cited to understand the principle or theory underlying the invention

"X" document of particular relevance

CERTIFICATION

Date of the Actual Completion of the International Search [2]

18 JUNE 1982

Date of Mailing of this International Search Report [2]

14 JUL 1982

International Searching Authority [1]

ISA/US

Signature of Authorized Officer [20]

David R. Sadowski

DAVID R. SADOWSKI

PCT/ISA/210 (second sheet) (October 1981)

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATIONS WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [10]

This international search report has not been established in respect of certain claims under Article 17(2) (a) for the following reasons:

1. [X] Claim numbers 4-7, 11-13, 16-18 and 22-24, because they relate to subject matter [12] not required to be searched by this Authority, namely:

Said claims fail to refer to previous claims in the alternative only, and said claims utilize multiple dependent claims as the basis for multiply dependent claims.

2. [ ] Claim numbers _____, because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out [13], specifically:

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING [11]

This International Searching Authority found multiple inventions in this international application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims of the international application.

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the International application for which fees were paid, specifically claims:

Remark on Protest

[ ] The [illegible]

[illegible]